Current Trends in Endocrinology
Vol. 6, 2012

Review

Control of postprandial hyperglycemia: How important is it in the prevention of diabetic complications

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ABSTRACT

Fasting blood glucose (FBG) ≥126 mg/dL (7 mmol/L) and/or glycosylated hemoglobin (HbA_1c) ≥6.5% have traditionally been used as a marker for the diagnosis of diabetes and initiation of a treatment plan. Despite the use of these diagnostic markers and a plethora of oral hypoglycemic agents, diabetic complications namely, cardiovascular disorders, renal failure and dialysis, and amputations, are on the rise. Therefore a reasonable concern is that either the definition of diabetes or the prevalent therapy with oral hypoglycemic agents, or both, are faulty. Abundant literature is available regarding the importance of using 2-hour postprandial glucose (2hPPG) in glycemic control for the prevention of diabetic complications. A robust association has been shown between 1-h or 2-h postprandial hyperglycemia (≥200 mg/dL; 11.1 mmol/L) and cardiovascular disorders and mortality. Notwithstanding the availability of such important information, 2hPPG control is still under-used in clinical practice of diabetes care. Worse than that, popularity of use of FBG and/or HbA_1c as a guide for diabetes care has permitted an incorrect diagnosis of Type 2 diabetes in numerous hypertensive patients treated with a thiazide diuretic and having elevated glucose levels followed by mistreatment with oral hypoglycemic agents. The result is subsequent development of overt diabetes in many individuals, some of them are riddled with numerous complications such as foot ulcer, gangrene, kidney failure or heart disease. This article is dedicated to redirecting the attention from using FBG and or HbA_1c to 2hPPG as a fundamental tool for evaluation of diabetes and to focus on therapy encompassing 2hPPG. Evidence has emerged from basic as well as clinical research claiming the importance of control of postprandial hyperglycemia in the prevention of diabetic complications. Prevention of diabetic complications is attainable by control of postprandial hyperglycemia with the prescription of a combination of Glargine insulin twice daily (12 hours apart) and treatment of glycemic excursions with fast-acting insulin.

KEYWORDS: postprandial, prevention of complications, glycemic control, HbA_1c, hyperglycemia

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INTRODUCTION

The word postprandial means after a meal; therefore, postprandial glucose (PPG) concentrations refer to plasma glucose levels after eating. In non-diabetic individuals, fasting blood glucose (FBG), after an overnight fast of eight to ten hours, generally ranges from 70 to 110 mg/dL (most laboratory normal ranges vary from 77 to 99 mg/dL) (4.2-5.5 mmol/L).

Glucose levels begin to rise 10 minutes after the start of a meal as a result of absorption of dietary carbohydrates. In non-diabetic individuals, plasma glucose concentrations peak 60 minutes after the start of a meal, rarely exceed 140 mg/dL (7.7 mmol/L), and return to pre-prandial levels within two to three hours due to a peak insulin response. In diabetes, peak insulin levels are delayed and are insufficient to control PPG excursions adequately. In diabetes, abnormalities in insulin and glucagon secretion, hepatic glucose production, and peripheral glucose uptake contribute to higher and more PPG excursions than in non-diabetic individuals. In general, a measurement of plasma glucose 2 h after the start of a meal is practical, generally approximates the peak value in patients with diabetes, and provides a reasonable assessment of postprandial hyperglycemia [1].

In the progression of diabetes, hyperglycemia occurs initially in the postprandial period (impaired glucose tolerance), while fasting blood glucose (FBG) remains normal. The incidence of diabetic microvascular complications, particularly retinopathy, has been shown to increase sharply with postprandial glucose (PPG) levels above 155 mg/dL (8.6 mmol/L), when FBG are below the diagnostic threshold of diabetes [2]. Furthermore, impaired glucose tolerance is recognized as an independent risk factor for cardiovascular morbidity and mortality [3]. Eventually, as insulin release continues to decline, overt diabetes with fasting hyperglycemia develops [4].

The relationship among FBG, PPG, and glycosylated hemoglobin (HbA_1c)

As HbA1c levels increase through the normal range (4% to 6%) and up to 8%, PPG levels increase to a greater extent and contribute more to HbA1c values than do FBG levels [5].

Plasma glucose levels pre-breakfast, pre-lunch, and 2- and 5-h post lunch were measured in diabetic patients and results were correlated with HbA1c levels. Multiple linear regression analysis indicated that only the 2- and 5-h post lunch plasma glucose levels correlated significantly and independently with HbA1c levels [6].

Postprandial hyperglycemia and diabetes complications

A common concern is to find a convenient way of assessing postprandial hyperglycemia. An oral glucose tolerance test (OGTT) has been primarily used in epidemiological studies that attempted to evaluate the risk of cardiovascular disease (CVD) associated with diabetes. The main advantage of the OGTT is its simplicity: a single plasma glucose measurement 2-h after a glucose load determines whether glucose tolerance is normal, impaired, or indicative of overt diabetes. The caveats of the OGTT is that 75 g glucose is never ingested during a regular meal and, more importantly, many events associated with ingesting a pure glucose solution do not incorporate the numerous metabolic changes associated with eating a mixed meal with many other nutrients. However, it has been demonstrated that the level of glycemia reached at 2-h after an OGTT is closely related to the level of glycemia after a standardized meal (mixed meal in the form of wafers containing oat-fractionation products, soy protein, and canola oil sweetened with honey; 10.7 g fat, 12.1 g protein, 8.9 g simple sugars, 41.1 g starch, and 3.8 g fibers). Therefore 2hPPG; levels after a breakfast in western countries (pancakes with syrup, sandwiches, grits) or after a lunch in eastern countries (rice, bread, vegetables, milk) can be considered equivalent to an OGTT.

Before detailing the importance of postprandial hyperglycemia in predicting diabetes complications, it is imperative to understand that 2hPPG has an even greater utility in identifying people with undiagnosed diabetes. These individuals may comprise a large proportion of diabetics, and may develop CVD. Diabetes is detected for the first time in many people who visit emergency departments for chest pain, by a random glucose level $\geq$200mg/dL (11.1 mmol/L). The 2hPPG is the most satisfactory screening method.

The sensitivity of 2hPPG, using a value of $\geq$200 mg/dL ($\geq$11.1 mmol/L) in detecting diabetes, is 97%; that is, only 3% of individuals with 2hPPG <200 mg/dL are considered to have diabetes. Specificity is 100% because all non-diabetic individuals have 2hPPG values <200 mg/dL. The positive predictive value is 100% because everyone with a 2hPPG value of >200mg/dL is considered

to have diabetes. FBG however is generally used for screening and indeed is recommended by the American Diabetes Association though it is an inadequate screening method [7].

In summary, the 2hPPG ≥200 mg/dL has high specificity, high sensitivity, and high positive predictive value. An FBG ≥140 mg/dL, which is generally used, has high specificity and positive predictive value but a sensitivity of 31% [7] which decreases the validity of this parameter in detecting diabetes. Numerous investigators have concurred in the validity of postprandial hyperglycemia in diagnosing diabetes and relating that to diabetes complications [7, 8, 9, 10, 11].

A dilemma in the diagnosis of diabetes

The antihypertensive drugs including thiazide diuretics, beta blockers (BB), calcium channel blockers (CCB), renin-angiotensin inhibitors such as angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) or vasodilators all produce varying degrees of elevated blood glucose levels above the normal laboratory range (70-99 mg/dL). This elevation of blood glucose or hyperglycemia is much more common with thiazide diuretics such as hydrochlorothiazide (HCTZ) or chlorthalidone than with BB, CCB, ACEI or ARB drugs. In addition, severe hyperglycemia, mimicking overt diabetes, is seen more commonly with thiazide diuretics than other antihypertensive drugs. Since hypertension is very prevalent in the population, hyperglycemia associated with antihypertensive therapy is equally prevalent. As a result, many of these patients are labeled with Type 2 diabetes and prescribed oral hypoglycemic agents. Hypertensive patients treated with diuretics constitute a huge population with many of them showing hyperglycemia thus contributing to the assumption that diabetes is epidemic. Therefore the end points associated with hypertension are difficult to distinguish from those associated with diabetes. In this regard, it is important to know that many patients with diuretic-induced hyperglycemia indeed do not have overt diabetes.

Here is one example in this puzzle.

Patient #1 - A 67 year old African American male was referred by a primary care physician and seen by the authors (AKM) in the office in November 2011 for renal insufficiency. He gave a history of hypertension for years and diabetes for nine months. He is a farm worker and is very active. Daily medication at the time of the first visit consisted of HCTZ 25 mg PO daily, glimepiride 2 mg PO daily, Lisinopril 40 mg PO daily, pravastatin 80 mg PO daily, amlodipine 10 mg PO daily, metoprolol 100 mg PO daily, and allopurinol 300 mg PO daily. During this visit he had a pulse of 66 beats/min and sitting and upright blood pressures (BP) were 130/90 mmHg. His physical examination was normal. The only available laboratory data at this visit was decreased estimated glomerular filtration rate (eGFR) of 42 mL/min (N = >60 ml/min). Changes in his medication at this office visit included discontinuation of Lisinopril, increase of amlodipine to 10 mg a.m. and 5 mg p.m. to improve BP control, and decrease of allopurinol 150 mg (due to decreased kidney function), and decrease of pravastatin to 40 mg PO daily. Fasting and 2-h basic metabolic panel (BMP), glycosylated hemoglobin (HbA_1c) and serum insulin levels were ordered. At his next visit, two weeks later, both the FBG (102 mg/dL) and 2hPPG (139 mg/dL) were normal. Serum creatinine (mg/dL) and eGFR (ml/min) for the corresponding periods were 1.73/42 and 1.66/44, respectively. The 2hPP serum insulin level was 126.5 µlU/L. Thus glucose levels are inconsistent with the diagnosis of diabetes. At best, a diagnosis of insulin resistance can be made. His kidney function was consistent with chronic kidney disease (CKD) Stage 2. At this time, he was advised to discontinue glimepiride, switch HCTZ to chlorthalidone 25 mg daily, increase amlodipine to 10 mg twice daily, and add potassium chloride 20 mEq daily to his therapy. At his third visit, six weeks later, his glucose levels for both FBG and 2hPPG were increased but still less than 200 mg/dL and thus still not consistent with the diagnosis of diabetes. He returned to the office in late March of 2012 with a laboratory done March 1, 2012. He is no longer taking glimepiride but taking thiazide diuretic chlorthalidone 25 mg/day to keep hypertension under control. His sitting and upright BP were 120/80 mmHg. FBG and 2hPPG decreased to 130 mg/dL and 152 mg/dL, respectively. His fasting insulin was normal

(16.7 μIU/ml) and his serum potassium was low (3.4 mmol/L) in both periods. Thus mildly elevated glucose levels, accompanied by decreased serum K are due to chlorthalidone. Hence potassium intake was increased to 20 mEq twice daily and the patient was advised to increase dietary potassium.

Thus here is a patient who went to a physician for treatment of hypertension. He was treated with a thiazide diuretic, beta blocker, calcium channel blocker and ACEI drugs. All of these antihypertensive drugs have been documented to produce hyperglycemia [11, 12,]. He developed hyperglycemia with an unspecified glucose level of 180 mg/dL (10 mmol/L) and HbA1c 6.2% noted in June 2011. Thus he was labeled to have developed Type 2 diabetes and placed on glimepiride, an oral hypoglycemic agent. Perhaps the primary care physician did not know that it is common to find hyperglycemia when a patient is treated with a thiazide diuretic, and glucose level is often reduced with correction of serum potassium. Therefore by definition, he does not have diabetes (2hPPG >200 mg/dL) [5, 7].

Two-hour postprandial hyperglycemia and cardiovascular disorders

Available data relating 2hPP hyperglycemia to endpoints in diabetes is slim with the exception of cardiovascular disorders. An abundant number of epidemiological studies and observations have identified a robust association of uncontrolled 2hpp hyperglycemia and coronary heart disease or death [8].

The DECODE analysis of data from 25,364 individuals reported that hazard ratios for death in individuals not previously known as diabetic, and with normal FBG, increased as 2hPPG increased. Over 7 years, the presence of impaired glucose tolerance doubled the risk of CVD and death but fasting hyperglycemia had no effect on CV mortality [13].

Pathophysiology of postprandial hyperglycemia

Different mechanisms have been described at the molecular level which are interesting to read but are complex and multifactorial. Hence their applications in day to day diabetes care are far from practical at this time.

From the viewpoint of diabetes care, it is important to understand that chronic elevation of FBG or 2hPPG can cause one or more of the following complications. These underlying complications are not in any particular order.

1. Retinopathy leading to partial or complete blindness.
2. Nephropathy leading to progressive renal failure and dialysis.
3. Neuropathy leading to urinary retention and foot ulcer, sexual dysfunction.
4. Vasculopathy leading to gangrene and amputation of digits or extremities, sexual dysfunction.
5. Coronary heart disease leading to myocardial infarction.
6. Neurogenic bladder leading to recurrent urinary tract infections.
7. Gastroparesis and paralytic ileus leading to recurrent vomiting, loss of nutrition and cachexia.

When patients present to a doctor's office with one complication, such as foot ulcers or gangrene, they usually have one or more additional complications. These complications are due to microvascular and macrovascular lesions caused by uncontrolled hyperglycemia. An important question is, what is the glucose threshold above which complications are likely to develop and below which complications are unlikely to develop. An even more important question is why glucose molecules in the normal range (80-100 mg/dL or 4.4-5.5 mmol/L) do not produce any complications but do so when the concentration increases to 200 mg/dL (11 mmol/L) or more. Therefore, a big question is: are glucose molecules the same or different in someone who is not diabetic versus one who is diabetic? Our previous research provides some insightful information about the mechanism of vascular injury caused by uncontrolled hyperglycemia. Research involving cell culture studies attest to the fact that elevated glucose levels, in and of itself, contribute to complications. In the laboratories initially in Dayton, Ohio, USA and later in Saskatoon, Canada, porcine vascular aortic endothelial cells were cultured and then treated with normal (90 mg/dL or 5 mmol/L) or high concentrations of glucose (540 mg/dL or 30 mmol/L) for a period of two,

six, or ten days. Additional cultured cells were treated with glucose at the same concentrations as above and insulin, or with glucose, insulin, and heparin.

Why were vascular endothelial cells chosen and not other cell types? There is good evidence in the literature that vascular endothelial cells are most vulnerable to injury by high blood glucose levels (hyperglycemia) [14]. High glucose levels bathe all the cells in the body. But why does damage occur in some cell types in diabetes? The answer is that most cells are able to reduce the transport of glucose inside the cells when they are exposed to high glucose levels, so that their internal glucose concentration remains constant. In contrast, the cells damaged by high glucose concentration are those that cannot retard transport of glucose inside the cells. Thus, in diabetes, endothelial cells and mesangial cells cannot reduce transport of glucose inside the cells when exposed to high glucose levels in the blood. In essence, a defect in membrane transport of endothelial cells permits excessive amount of glucose to enter inside the cells when glucose levels are high. Therefore, complications that develop in diabetes likely involve mechanisms involving excessive amounts of glucose inside the endothelial cells, rather than outside [14]. In our cell culture studies, we have demonstrated crystalline structures that are presumably glucose in severely damaged cells, as previously published [15]. Even endothelial cells that were treated with insulin and high glucose revealed telltale evidence of crystalline structures presumably glucose, as previously published [15].

Many hypotheses or pathways have been proposed to explain high glucose-induced cellular damage that persists and perpetuates damage to various organs and gives rise to clinically evident disease, such as retinopathy, heart attack, foot ulcer, gangrene, or kidney failure. None of the pathways thus far advanced explain damage to all the organs in a unified fashion. The authors propose a unified theory, which is ischemia (markedly reduced blood flow), which may explain damage to all organs. Reduced blood flow in an indolent fashion does not cause necrosis but causes atrophy. This is evident in heart as myocardial fibrosis and cardiomyopathy or atrophic tubules and interstitial fibrosis in kidneys. Progressive kidney failure in diabetes is more due to loss of tubules and interstitial fibrosis rather than glomerular sclerosis.

Inability to achieve penile erection is clearly due to lack of blood flow through the penile microvasculature. Reduced blood flow can be associated with increased vascular permeability, resulting in exudation of plasma proteins in the free surface outside of the vessels. This is best seen as hemorrhages and exudates in the retina of eyes and as protein leak from kidney glomeruli in diabetes. Reduction of high blood glucose to normal or near normal levels with insulin results in mitigation of endothelial damage and repair, consequently, partial or complete recovery of organ function. Like these authors, other authors have considered that diabetes-specific microvascular disease in the eyes (retina), kidney glomeruli, and *vasa nervorum* (small vessels surrounding nerves in feet and penis) have similar pathophysiologic features [14].

Still, other authors found from experiments in rats that protein leak in urine or proteinuria is due to excessive filtration pressure of the kidney glomeruli caused by high glucose levels or breakdown of the filter in the glomerulus. Further, these authors determined that this excessive filtration pressure causes glomerular sclerosis and kidney failure. Based on this theory, these authors proposed that angiotensin-converting enzyme inhibitors and, subsequently, angiotensin receptor blocker drugs can reduce filtration pressure of kidney glomeruli and in so doing reduce the risk of glomerular sclerosis and kidney failure [16]. The greatest pitfall of this theory is why will high glucose levels cause damage to the kidneys in a manner that is entirely different from its adverse effect on other organs such as the heart, eyes or feet.

Fundamentally, the bad effects of high glucose level will be felt uniformly in all organs as considered by these authors, and other authors [14]. Once again, the uniformly negative effect of high blood glucose is necrosis of vascular endothelial cells, sloughing off of these cells into the capillary lumen forming microthrombi along with cholesterol and platelet deposits resulting in

occlusion of capillaries with slight or no blood flow to the organs.

Thus, cell culture experiments done by these authors have paved the way to a better understanding of the pathogenesis of diabetic complications and how these complications can be adequately prevented.

The exact mechanisms of injury to the vascular endothelial cells and tubular epithelial cells caused by high glucose levels are not yet fully elucidated. Some authors have shown that high blood glucose levels increase oxidative stress and increase the production of reactive oxygen species [17, 18].

We have considered that toxic oxygen radicals may be involved in ischemic injury to the organs and we designed an experiment to determine that. Glutathione is an important enzyme for oxidative stress. Therefore, by inhibiting glutathione, oxidative injury may increase. We treated vascular endothelial cells with a potent glutathione inhibitor, buthionine sulfoxamine, for two and six days. After six days of treatment, endothelial cells had undergone severe necrosis beyond recognition. Thus, this experiment suggests that deficiency of glutathione may be an important mechanism of diabetic microvascular complications.

Our cell culture studies have helped us to determine the mechanism of protection against high glucose-induced cellular damage. We treated the cultured endothelial cells with insulin and with insulin and heparin in the presence of high glucose level in the culture medium. We noted slight or no morphological damage to cells, as previously published [15]. We have postulated that insulin reduces oxidative stress [18]. Heparin seems to be additive to insulin in that effect [19].

There is one mechanism by which heparin may synergize insulin. We have found that high glucose as well as insulin increases endothelin-1 production in the cultured endothelial cells. Endothelin-1 is a potent vasoconstrictor and can aggravate ischemic injury to the endothelial cells. Heparin is a potent inhibitor of endothelin-1. Therefore, by inhibiting endothelin-1 production, heparin may synergize insulin effect in protection against high glucose-induced cellular injury [19].

The Diabetes Complications and Clinical Trial (DCCT) established glycosylated hemoglobin (HbA_1c) as the gold standard of glycemic control, with levels $\leq$7% deemed appropriate for reducing the risk of vascular complications. Yet, even HbA_1c levels were comparable between intensively treated subjects and their conventionally treated counterparts, the latter group experienced a markedly higher risk of progression to retinopathy over time. In addition, attempts to reduce HbA_1c $\leq$7% with high dose insulin resulted in a high risk of causing hypoglycemia. A speculative explanation was made that hyperglycemia-induced oxidative stress is the chief underlying mechanism of glucose-induced vascular damage [20].

It was further stated that both postprandial state and glucose levels throughout the day may be an important but underappreciated mechanism resulting in accumulation of reactive oxygen species and micro and macro vascular disease acceleration. The phenomenon of “hyperglycemic memory” also exists whereby hyperglycemia-induced microvascular changes persist or even progress during subsequent periods of normoglycemia [21].

Control of hyperglycemia

Overall, since hyperglycemia or a high glucose level is the culprit of diabetic complications, lowering of high glucose level by therapy is the logical answer for prevention of its complications.

High blood glucose levels can be lowered by oral antidiabetic agents, insulin injections, a combination of both, or dialysis against a glucose-free bath. The latter was never put in practice except for those who are on dialysis for end stage kidney failure. It is evident in the literature that lowering of high blood glucose levels can prevent diabetic microvascular and macrovascular complications. No systematic studies were done to unequivocally show that simple lowering of high glucose levels by oral antidiabetic agents, such as glyburide, metformin, or Januvia will prevent diabetic complications, as already stated. Occasional studies showed that use of metformin alone, or metformin in combination with insulin in Type 2 diabetes reduced the risk of myocardial infarction [22]. The most important caveat of Type 2

diabetes is that some of the patients in this type of trial probably did not have diabetes but had diuretic-induced hyperglycemia [23]. Further, Type 2 diabetes was never defined appropriately, such as by 2-h postprandial glucose level or glucose tolerance tests. In diabetics where 2-h postprandial glucose is above 200 mg/dL (>11.1 mmol/L), oral antidiabetic agents can be used in addition to insulin to achieve better glucose control than either alone. However, the primary outcomes, such as microvascular complications, are not affected, despite improved glucose control. Two studies are cited to that effect.

1. 390 patients treated with insulin in the outpatient clinics of three hospitals for a period of 4.3 years received metformin (850 mg) or placebo (1-3 times daily). The primary end point was an aggregate of microvascular and macrovascular morbidity and mortality, as separate aggregate scores. Metformin treatment prevented weight gain, improved glycemic control, and reduced insulin requirement but didn't improve the primary end points. Metformin did, however, reduce the risk of macrovascular disease after a follow-up period of 4.3 years [24].

2. In an unpublished study from Kolkata, India, by one of the authors and Dr. Aswini Patnaik, 312 patients with diabetes were treated with insulin, oral hypoglycemic agents, or a combination of both. Paired fasting glucose and 2hPP glucose, and eGFR were obtained before and after a 12-month period. Percentage decrease in glucose levels were greater in the group treated with insulin and oral hypoglycemic agents, but eGFR percentage change was significantly higher in the insulin alone group than in the other two groups.

In the authors cell culture studies, when cells were treated with glucose and insulin, the glucose measurement in culture medium showed slight or no change in glucose concentration, although morphologically cells appeared healthier than cells treated with glucose alone. This finding suggests that insulin has a protective effect, which may be independent of simply lowering of glucose [15]. Thus, combining clinical studies with the adjunct of cell culture studies, it is prudent to state that insulin is the cornerstone of therapy for protection of EC integrity and hence mitigation of clinical complications. On the other hand, there is no shred of evidence to indicate that prevention of diabetic complications can be accomplished by simply lowering of glucose levels with oral antidiabetic agents alone.

The findings of our cell culture studies provide strong support to clinical observations on glycemic control. Most clinical studies are limited to heart health; only a few are available in other areas such as renal failure and dialysis, or amputation [25].

This study has focused on renal protection in diabetes. Our hypothesis is that glycemic control with intensive insulin therapy is fundamental to renal protection in diabetes.

Renal protection in diabetes

The author and collaborators feel that lowering of blood glucose levels to near normal levels in diabetes is a reality. However, trying to lower blood glucose levels to normal level with intensive insulin therapy is associated with a high risk of hypoglycemic reactions. Further, there is no evidence to indicate that keeping the glucose level at normal levels will prevent cellular injury or repair any damage that has already incurred. Therefore the goal of adequate glycemic control is to keep 2hPPG at an optimal level which will not produce hypoglycemia. Avoiding hypoglycemic reactions is an integral part of uneventful diabetes care. Hypoglycemia is a fearful experience which will distract patients to adhere to insulin injections. There is no yardstick available in the literature to determine optimal glycemic levels which will confer renal protection. However, there is subtle evidence that 2hPPG >200mg/dL (11.1 mmol/L) is associated with a significant decrease of glomerular filtration rate (GFR) whereas keeping 2hPPG of <200mg/dL (<11.1 mmol/L) gives rise to insignificant changes in renal function [26].

We have noted with elevation of glucose levels to >200 mg/dL (>11.1 mmol/L) at 2h postprandial period is associated with a discernible increase of serum creatinine (Scr) and decrease of eGFR when sampled at the same time. The changes are not notable when 2hPPG rises to <200 mg/dL (<11.1 mmol/L). A patient is presented to illustrate this observation.

A 78 y white Canadian male came to author's (AKM) office as a self-referral for diabetes control. He is of average build, younger looking than his age, and very active. He also gave history of hypertension. He was treated with oral antidiabetic agents and Lisinopril which were gradually discontinued and he was started on insulin therapy. He was admitted to a local hospital for shortness of breath. Myocardial infarction was considered but could not be documented. His latest visit in June 2012 reveals that he feels well and has no complaint. Office examination showed blood pressure sitting 140/60 mmHg and standing 140/50 mmHg with a pulse of 62/min and regular. Heart auscultation revealed systolic and diastolic murmur grade 2/6. His current treatment consists of insulin Glargine (Lantus®) 15 units subcutaneously after breakfast and 15 units after dinner. For hypertension control he takes spironolactone 25 mg PO two times daily and chlorthalidone 12.5 mg PO daily. Other medicines include magnesium oxide 400 mg PO TID and antilipidemic drug 20 mg PO at bedtime. His laboratory is shown below.

Laboratory						
	Glucose mg/dL mmol/L)		Scr mg/dL		eGFR ml/min	
June 13, 2012	F	2hPP	F	2hPP	F	2hPP
	114	235	1.18	1.28	>60	58
Dglucose (2hPP – F) 121						
F = Fasting. 2hPP = 2h PostPrandial						
24 hour urine protein was < 111 mg and creatinine clearance 67.7 ml/min						

In order to reduce 2hPPG to less than 200 mg/dL, Glargine insulin was increased to 20 units after breakfast but dinner dose remained unchanged.

In order to validate this observation, data of FBG and 2hPPG and corresponding Scr and eGFR from 56 adults with diabetes were analyzed. In our sample of 56 (29 female and 27 male), ages ranged from 19 to 91 years with a mean of 68.7 $\pm$ 13.5 years. Diagnosis of diabetes was confirmed by 2hPPG $\geq$200 mg/dL (11.1 mmol/L). FBG, 2hPPG, and a renal function panel which included BUN, Scr and eGFR were prospectively obtained as a part of the routine laboratory tests for regular office visits. eGFR was calculated from the modification of diet in renal disease equation as recommended by the National Kidney Foundation [27].

Before diagnosis of diabetes was established, it was affirmed that no patients were taking thiazide diuretics, which causes or aggravates hyperglycemia mimicking diabetes [23]. All patients were treated with a combination of short-acting insulin, on a sliding scale, and long-acting insulin either NPH or Lantus®.

Hypertension was treated with one or more of the combination of antihypertensive drug groups. These are beta blockers, namely atenolol or metoprolol; second generation dihydropyridine calcium channel blocker, namely amlodipine or isradipine; sympathetic inhibitor, namely alpha methyldopa; and diuretic, namely HCTZ in resistant hypertensive patients. The most common combination of antihypertensive drug therapy used was atenolol and amlodipine. d levels (2hPP - F) for glucose, Scr and eGFR were calculated for each patient. Pearson correlation coefficients were calculated to determine if the changes in renal function (dScr and deGFR) were related to changes in glucose levels between F and 2hPP time points (dglucose). The regression analysis

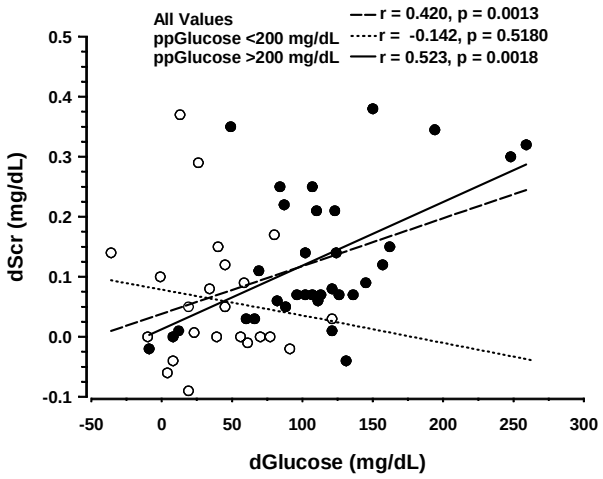

Figure 1A. Correlation of dScr (2hPP – F) with dglucose (2hPP – F). Correlation between dScr and dglucose and correlation coefficients and *p* values are shown for all 56 patients (dashed line, all data points), for patients whose 2hPP glucose is greater than 200 mg/dL (solid line, black circles, *n* = 33) and for patients whose 2hPP glucose is less than 200 mg/dL (dotted line, open circles, *n* = 23). Reprinted from Mandal, A. K., Hiebert, L. M. and Khamis, H. 2011, Diab. Res. Clin. Pract., 91, 190-194 with permission from Elsevier.

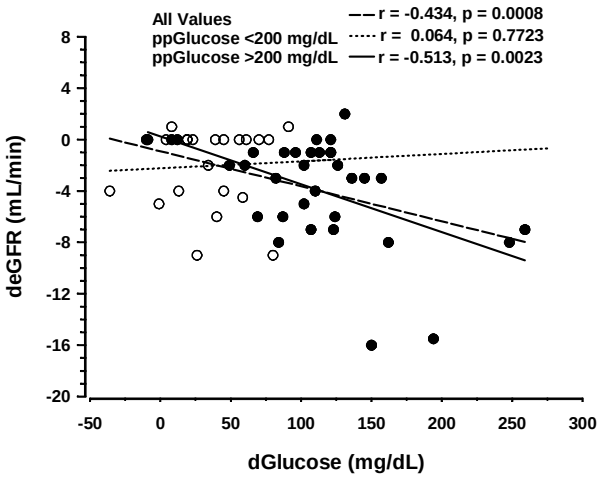

Figure 1B. Correlation of deGFR (2hPP – F) with dglucose (2hPP – F). Correlation between deGFR and dglucose and correlation coefficients and *p* values are shown for all 56 patients (dashed line, all data points), for patients whose 2hPP glucose is greater than 200 mg/dL (solid line, black circles, *n* = 33), and for patients whose 2hPP glucose is less than 200 mg/dL (dotted line, open circles, *n* = 23). Reprinted from Mandal, A. K., Hiebert, L. M. and Khamis, H. 2011, Diab. Res. Clin. Pract., 91, 190-194 with permission from Elsevier.

between dglucose and dScr, and dglucose and deGFR are presented in Figures 1A and 1B, respectively.

For every 100 mg/dL increase in dglucose, the dScr increases by 0.08 mg/dL and deGFR decreases by 2.73 ml/min. Therefore, an increase in glucose between F and 2hPP time periods is significantly correlated with an increase in serum creatinine and decrease in eGFR. We have enhanced the predictive value of 2hPPG by developing the parameter of dglucose (2hPPG – FBG). Thus dglucose is a stronger predictor than 2hPPG. In this study, analyses are based on a sample size of 56, insuring reliable detection of important effects. Our data are in agreement with a previous study [26] and further stress that 2hPP $\geq$200mg/dL (11.1 mmol/L) or dglucose >100 mg/dL is determinant of renal function deterioration. In this initial observation, we have documented that in patients whose 2hPPG is greater than 200 mg/dL, for every 100 mg/dL increase in dglucose, dScr increases by 0.11 mg/dL and deGFR decreases by 3.73 ml/min, while in patients whose dglucose <200 mg/dL for every 100 mg/dL increase in dglucose little change is seen in dScr (-0.04 mg/dL) or deGFR (+0.54 ml/min) (Figures 1A and 1B). Average glucose and HbA_1c were poorly correlated with fasting renal function parameters and showed low *r* and insignificant *p* values (Table 1) [28].

Since we have observed that renal function change is insignificant by keeping 2hPPG <200 mg/dL with intensive insulin therapy, we have started to examine the long-term effect of intensive glucose control as above on progression of renal function change in diabetes. Diabetic nephropathy is the most common cause of end stage renal disease (ESRD) throughout the world. ESRD requiring dialysis is a major cost driver for the healthcare industry and insurance companies. We have asked an important question: Can progression of chronic kidney disease (CKD) be prevented by adequate glycemic control with intensive insulin treatment? Many studies in the past have documented benefits of glucose control in prevention of microvascular and macrovascular complications

Table 1. Correlation coefficients and *p* values for HbA1c or average glucose and fasting BUN, Scr and eGFR. (Adapted from Mandal, A. K., Hiebert, L. M. and Khamis, H. 2011, Diab. Res. Clin. Pract., 91, 190-194 with permission from Elsevier).

	HbA1c		Average glucose	
	Correlation coefficients (*r*)	*p* values	Correlation coefficients (*r*)	*p* values
F BUN	0.137	0.3987	0.135	0.4455
F Scr	0.233	0.1485	0.275	0.1152
F eGFR	-0.127	0.4360	-0.169	0.3401

F = fasting, Scr = serum creatinine, eGFR = estimated glomerular filtration rates.

in diabetes [29-32]. However, no study has systemically examined if intensive glycemic control reduces the risk of progression of diabetes-related CKD. Further, there is little evidence indicating that control of 2hPP hyperglycemia is effective in reducing the progression of CKD. Most importantly, prevention of progression of CKD will reduce the incidence of ESRD and allow life without dialysis treatment. Our on-going long-term study points toward attaining that goal (unpublished).

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